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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,237	HACKETT ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-102* is/are pending in the application.

4a) Of the above claim(s) *5-12,14-18,36,38-40,44-84 and 96-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,13,19-35,37,41-43,85-95 and 102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/04,11/05,5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 15 January 2004, which claims benefit of US Provisional application 60/440,125, filed 15 January 2003. The preliminary amendment filed 16 June 2006 has been entered. Claims 1-102 were originally filed. Claim 85 was amended in the 16 June preliminary amendment. Claims 1-102 are pending.

Election/Restrictions

Applicant's election of Group I, the insulator species DHS5 site of a chicken β-globin locus and the cell species hepatocyte in the reply filed on 16 June 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 44-84, 96 and 97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and claims 5-12, 14-17, 36, 38-40 and 98-101 are withdrawn as being drawn to nonelected species[1], there being no allowable generic or linking claim. Election was made **without** traverse in the 16 June reply.

Claims 1-4, 13, 19-35, 37, 41-43, 85-95 and 102 are presently under consideration.

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[1] It is noted that although Applicant indicates that 98-101 read on the elected species, Applicant does not include claims 5-8, which recite the same SEQ ID NO as claims 98-101, among the claims reading on the elected species. Furthermore, based on the data provided in Table I, it appears that SEQ ID NO: 16, 17, and 18 are not present in the elected insulator. (SEQ ID NO: 16 appears to be the human 5' HS5 CTCF binding site, SEQ ID NO: 17 appears to be the human 3' HS1 CTCF-binding site and SEQ ID NO: 18 appears to be the mouse 3' HS1 CTCF-binding site.

Sequence Data

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Appropriate correction is required.

Claim Objections

Claim 13 is objected to because of the following informalities: The claim text is misformatted such that the character following the word "chicken" in line 2, which should presumably be the Greek letter β, is an open box. Appropriate correction is required.

Claim Construction

Claims 85-87, 91-95 and 102 are directed to a transposon comprising a transcriptional unit and "a means for preventing regulation of transcription of host nucleic acid by the transcriptional unit following insertion into a mammalian cell". The limitation is interpreted to invoke 35 USC §112, sixth paragraph, and will be construed accordingly.

It is noted that although claims 88-90 depend from claim 85, the claims recite structural elements modifying the "means for" sufficient for achieving the specified function (i.e., "CTCF binding site" or "insulator element"). As such structural modification of the "means for" is not consistent with the requirements for invoking 35 USC §112, sixth paragraph, the Office will not

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For these reasons, it is presumed that the exclusion of claims 5-8 from the claims reading on the elected species is correct and claims 98-101 also read on non-elected species.

apply 35 USC §112, sixth paragraph, in examining claims 88-90. See MPEP 2181, prong "(C)" of the 3-prong analysis.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27, 29-35, 37, 41-43, 93 and 95 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed to a genetically modified cell, wherein the cell encompasses a cell present in a human being as evidenced by claims 30 and 95. Thus, the broadest reasonable interpretation of the claim clearly encompasses a cell that might be present or is intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 85-87, 91-95 and 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the requirements of 35 USC §112, sixth paragraph, if one skilled in the art would not be able to identify the structure, material or acts for performing the recited function from the description, then applicant will be required to amend the specification to include the material incorporated by reference and to clearly link or associate the structure, material or acts to the function recited in the claim. See 35 U.S.C. 112, sixth paragraph ("An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof." (emphasis added)); see also *B. Braun Medical*, 124 F.3d at 1424, 43 USPQ2d at 1900 (holding that "pursuant to this provision [35 U.S.C. 112, sixth paragraph], structure disclosed in the specification is corresponding' structure only if the specification or prosecution history clearly links or associates that structure to the function recited in the claim. This duty to link or associate structure to function is the quid pro quo for the convenience of employing 112, paragraph 6."); *Medical Instrumentation and Diagnostic Corp. v. Elekta AB*, 344 F.3d 1205, 1218, 68 USPQ2d 1263, 1268 (Fed. Cir. 2003)(Although one of skill in the art would have been able to write a software program for digital to digital conversion, such software did not fall within the scope of "means for converting" images as claimed because nothing in the specification or prosecution history clearly linked or associated such software with the function of converting images into a selected format.); *Wolfensperger*, 302 F.2d at 955, 133 USPQ at 542

(just because the disclosure provides support for a claim element does not mean that the USPTO cannot enforce its requirement that the terms and phrases used in the claims find clear support or antecedent basis in the written description).

The discussion commencing at p. 10, ¶2 and continuing through the second paragraph on page 21 provides a generic description of evidence in the literature indicating that insulator elements exist in matrix attachment regions. The specification discusses the chromatin structure including cytological studies suggesting that chromosomes are divided subdivided into domains manifested as loops anchored to a network of proteins called the nuclear matrix or nuclear scaffold (¶ bridging pp. 10-11); discusses the isolation of nuclear matrix proteins and identification of matrix attachment regions (MARs; ¶ bridging pp. 11-12); discusses variability in the structure of MARs (¶ bridging pp. 12-13); discusses biochemical evidence supporting the division of chromatin into transcriptionally active and inactive domains (¶ bridging pp. 13-14); cites studies of A-elements in MARs, stating "[t]here is a significant body of research that describes the functional, structural, and detailed features of A-elements so that a person of ordinary skill in the se arts is able to identify A elements" (p. 15, ll. 8-10); discusses MAR-like sequences identified at the boundaries of the DNase-sensitive regions of the human β-interferon gene, stating "it is known that some MARs, and A-elements, contain insulator elements that satisfy the test criteria for an insulator element" (p. 17, ll. 1-3); cites papers describing *scs/scs'*-elements, the *su(Hw)* binding region, and the β-globin DHS5 site as teaching DNA sequences capable of alleviating position effects in transgenic fruit flies (¶ bridging pp. 17-18); identifies the CTCF-biding site as a mediator of enhancer blocking (p. 20, ll. 5-9); and cites references teaching the *sns* insulator, sequence flanking the sea urchin H2A histone gene, the *Drosophila*

Fab-7 sequence, the MAR sequence flanking the mammalian tyrosinase gene and an insulator sequence found in the *H19/Igf2* locus as other examples of insulator elements.

In the first full paragraph on page 21, the specification teaches the common features of insulator elements are: typically active only when part of chromatin; do not alter expression levels of genes in transient assays; do not alter tissue specificity of transgene expression; and MARs block enhancer activity but do not have silencing-blocking activity.

Viewed as a whole, the specification discloses the structure corresponding to a means for preventing regulation of transcription of a host nucleic acid by a transcriptional unit in broad generic terms and the specific details are incorporated by reference to numerous publications in the non-patent literature. The skilled artisan would not be able to identify the structure or material for performing the recited function based on the disclosure. Therefore, applicant must amend the specification to include the material incorporated by reference and clearly link or associate the structure or material to the function recited in the claim. See MPEP 2181.

Claims 3, 4, 23, 26, 41-43 and 95 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 are indefinite in reciting, "the insulator element". Claim 1, from which the claims depend, recites that the transposon comprises "a plurality of insulator elements". It is unclear, therefore, whether "the insulator element" of claims 3 and 4 refers to a single insulator element or to all of the insulator elements of the base claim. Amending the claim to recite, e.g.,

"wherein one or more insulator elements..." instead of "wherein the insulator element..." would overcome this rejection.

Claim 23 is indefinite in reciting that the nucleic acid is a member of the group, wherein only a single member is recited (i.e., DNA encoding an mRNA). It appears that Applicant views DNA encoding an mRNA as a Markush group comprised of multiple distinct members; however, it is unclear precisely what defines and distinguishes the alternative members that make up the group.

Claim 26 is indefinite in reciting "the suicide sequence nucleic acid". There is no antecedent for a "suicide sequence nucleic acid in claim 13, from which claim 26 depends.

Claim 26 is further indefinite in reciting that the suicide sequence comprises "an independent promoter". The metes and bounds of the claim are unclear because the claim does not specify what the promoter is independent from. The claimed transposon might comprise multiple elements (e.g., insulators, marker genes, etc.) and limitation of the promoter to being independent of any one of these elements results in a claim of significantly different scope from a claim requiring that the promoter be independent of any other element. Therefore, the metes and bounds of the claim as a whole are unclear.

Claim 41 is indefinite in reciting, "the protein is a marker". There is no antecedent basis for a "protein marker" in claim 32, from which the claim depends.

Claim 42 is indefinite in depending from claim 41.

Claim 43 is indefinite in reciting, "the therapeutic protein". There is no antecedent basis for a "therapeutic protein" in claim 34, from which the claim depends.

Claim 95 is indefinite in limiting the cell of claim 94 to being in a human. As the cell of claim 94 is limited to *in vitro*, there is no antecedent for a cell in a human in claim 94.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 13, 19-21, 23, 27, 29, 31-35, 41-43, 85-93 and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Chung et al. (1997) US Patent No. 5,610,053 (made of record in the IDS filed 9 July 2004) as evidenced by Pirrotta (1988) *Biotechnology* 10:437-456 and Melcher U. Molecular Genetics, Updated 4 February 2006, http://opbs.okstate.edu/~melcher/MG/MGW3/MG32217.html, p. 32217.

Independent claim 1 is directed to a transposon comprising a transcriptional unit and a plurality of insulator elements, wherein the transcriptional unit is flanked by at least one insulator element on each side of the transcriptional unit, wherein the transcriptional unit comprises an exogenous nucleic acid for introduction into a cell. Independent claim 85, is directed to a transposon comprising a transcriptional unit and a means for preventing regulation of transcription of host nucleic acid by the transcriptional unit following insertion into a host mammalian cell.

In example 7 (commencing in col. 28) Chung et al. teaches construction of a plasmid comprising the fruit fly white minigene flanked by insulator elements derived from the chicken

β-globin gene. Chung et al. further teaches that the minigene/insulator construct is cloned into the EcoRI site of the pCasper W15 vector, thereby inserting the miningen into the P-element transposon. (See Pirrotta et al., Figure 22-3.) Thus, the construct of Chung et al. comprises a transposon comprising a transcriptional unit (white minigene) flanked by chicken β-globin insulator elements according to the limitations of claim 1. Further, Chung et al. teaches that the insulator elements disclosed therein "not only insulate a transfected gene or genes from the influences of DNA surrounding the site of integration, but would also prevent the integrated constructs from impacting on the DNA at the site of integration and would therefore prevent activation of the transcription of genes that are harmful or detrimental to the cell." (Bridging col. 11-12.) Thus, Chung et al. teaches that the insulator elements are a "means for preventing regulation of transcription of host nucleic acid by the transcriptional unit". It is further noted that the instant application identifies the insulator element in the 5' hypersensitive site of the chicken β-globin gene as a means according to the invention in the paragraph bridging pp. 19-20 of the specification, which is the same as the insulator elements used by Chung et al. (See especially col. 4, ll. 54-67.)

Thus, Chung et al. anticipates the limitations of independent claims 1 and 85. Furthermore, the construct of Chung et al. comprises each of the elements of dependent claims 2-4, 13, 19-21, 23, 27, 29, 31-35, 41-43, 86-93 and 102. Melcher evidences that the P-element transposon of Chung et al. comprises inverted terminal repeats according to claims 2, 19 and 90. (See under the heading "Interpretations" in Melcher.) The discussion of the chicken β-globin insulator in the paragraph bridging pp. 19-20 evidences that the insulator of Chung et al. comprises CTCF-binding sites according to the limitations of claims 3, 4, 88 and 89. The

insulator element of Chung et al. is from a DHS5 site of a chicken β-globin locus according to claim 13. (Id.; see also the description of the DHS5 site from the chicken β-globin locus at p. 17, ll. 16-17 of the instant application, which cites the work of Chung et al. (ref. 23).)

The miniwhite gene of Chung et al. comprises a promoter according to claims 20 and 91, as evidenced by expression in transgenic *Drosophila* (Example 7), which is used as a marker according to claims 21, 23, 41 and 92, and comprises exogenous nucleic acid, which is DNA according to claims 87 and 102. Further, the transgenic *Drosophila* of Chung et al. would comprise cells comprising the transposon, which cells anticipate the cell of claims 27, 29 and 93; and, because there is no evidence that the various processes for introducing a nucleic acid into a cell recited in claims 31-35 would impart an identifiable, distinctive structural characteristic to the final product, the cells of Chung et al. also anticipate the cell of claims 31-35.

Claims 42 and 43 limit the protein expressed from the transcriptional unit to being therapeutic and ameliorating a medical condition. As the specification does not provide a definition of "therapeutic" or "medical condition" and the white gene of Chung et al. corrects a genetic defect in the transgenic flies, the protein expressed from the white gene reads on the protein of claims 42 and 43 according to the broadest reasonable interpretation thereof.

Finally, as discussed above, Chung et al. teaches that the insulator elements would prevent activation of "genes" by the constructs, which teaching anticipates the limitations of claim 86.

Thus, Chung et al. teaches a transposon comprising all of the elements of the invention presently claimed. Therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by Chung et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 13, 19-21, 23-35, 37, 41-43, 85-95 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hackett et al. (1998) WO 98/40510 in view of Chung et al. (*supra*).

The limitations of independent claims 1 and 85 are described herein above. Hackett et al. teaches a transposon comprising a transcriptional unit comprising exogenous DNA for introduction into a cell. (See especially p. 14, ¶2; p. 21, ¶2; ¶ bridging pp. 22-23; p. 30, ¶2). Hackett et al. further teaches that the transposons disclosed therein are to be used to deliver nucleic acids into isolated or cultured cells (see, e.g., ¶ bridging pp. 22-23), in processes of gene

therapy (see especially ¶ bridging pp. 27-28) and in the production of transgenic animals (see especially ¶ bridging pp. 30-31).

Hackett et al. does not teach that the transposon comprises insulator elements or a means for preventing regulation of transcription of host nucleic acid by the transcriptional unit.

As described herein above, Chung et al. teaches an insulator element from the chicken β-globin locus and its use in constructs for introducing exogenous nucleic acid into cells. Chung et al. further teaches that the preferable placement of the insulator elements is on both sides of a gene (i.e., flanking; see especially col. 10, 56-63). Still further, Chung et al. teaches that the use of insulator elements as described therein is particularly advantageous in the production of transgenic animals and in gene therapy applications. (See, e.g.: col. 10, ll. 28-32 ("By insulating a gene or genes introduced into the transgenic animal, the expression of the gene(s) will be protected from negative or inappropriately positive regulatory influences in the chromatin at or near the site of integration."); bridging col. 11-12 ("The constructs of the invention would not only insulate a transfected gene or genes from the influences of DNA surrounding the site of integration, but would also prevent the integrated constructs from impacting on the DNA at the site of integration and would therefore prevent activation of the transcription of genes that are harmful or detrimental to the cell."); col. 23, ¶3 ("By insulating a gene to be transfected with the insulator element of the present invention, the gene could be maintained in an active state." Thereby, overcoming one of the main problems of current gene therapy techniques.); col. 23, ¶4 ("Another problem of gene therapy is the danger that the enhancer or regulatory element of the transfected gene, when integrated in close proximity to an oncogene, may actually promote tumor formation. Again, by insulating the transfected gene with the chromatin insulator element

of the invention, the enhancer or regulatory elements of the transfected gene may be prevented from influencing the expression of critical endogenous genes whose activities may be harmful or detrimental to the host."); col. 23, ¶5 ("[T]he insulator element should be useful for making transgene animal expressing certain gene products at various levels and/or at particular times in development. Further, the constructs of the invention, used in the production of transgenic animals, would circumvent the problems encountered when DNA introduced into the animal cells or embryos becomes integrated in nonexpressing or silent areas of the chromatin."); and ¶ bridging col. 23-24 ("The insulator element also promises to be a useful tool...in the production of stably transfected cell lines. Most frequently, integration of a transfected gene or construct into host cell genome occurs at random. Because the expression of a stably transfected gene is influenced by adjacent regulatory elements near the site of gene integration, insulating the transfected gene with the insulator elements of the present invention eliminates the variability that is caused by cell-to-cell differences in integration position and in the random sites of integration.")

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transposon taught by Hackett et al. by the inclusion of a chicken β-globin insulator element flanking the transcriptional unit as taught by Chung et al.

Motivation to combine the elements taught in the prior art comes from the teachings of Hackett et al. indicating that the transposons described therein are to be used in the production of transformed cells and transgenic animals and in gene therapy, and comes from the teachings of Chung et al. indicating that the inclusion of insulator elements provides a number of advantages in each of the intended uses identified by Hackett et al. Absent evidence to the contrary, one

would have a reasonable expectation of success in combining the technologies in view of the effectiveness of the insulator element of Chung et al. in various constructs, including a transposon. (Id.)

For these reasons, the invention of independent claims 1 and 85, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims 2-4, 13, 19-21, 23-35, 37, 41-43, 86-95 and 102 are also found in the cited art. As described above, the insulator element of Chung et al. comprises each of the limitations of claims 3, 4, 13, 19, 88, 89 and 90.

The transposon of Hackett et al. comprises at least two inverted repeats according to claim 2 (see especially p. 12, ¶2), which repeats bind sleeping beauty (SB) transposase according to claim 24 (see especially p. 12, ll. 10 *et seq.*). Further, Hackett et al. contemplates a variety of transcriptional units including transcriptional units comprising: a promoter and/or enhancer according to claims 20 and 91 (¶ bridging pp. 27-28); a marker according to claims 21, 41 and 92 (*i.e.*, any of the gene products recited in the ¶ bridging pp. 27-28 could be used as marker); a sequence encoding an mRNA according to claim 23; a sequence encoding a therapeutic protein according to claims 42 and 43; an exogenous nucleic acid according to claim 87; and a DNA according to claim 102.

Both Hackett et al. and Chung et al. contemplate using constructs comprising the elements disclosed therein to produce cells comprising the constructs, which for the reasons discussed herein above with respect to anticipation by Chung et al. render obvious the cells of claims 27, 29, 31-35 and 93. Furthermore, both Hackett et al. and Chung et al. contemplate introduction of the constructs into cultured cells according to claims 28 and 94 and contemplate

gene therapy, which renders obvious the cell in a human of claims 30 and 95. (See *supra*.) In addition, at p. 23, l. 14, Hackett et al. contemplates introducing the construct into a hepatocyte according to claim 37 and, according to the teachings Chung et al., the construct would prevent regulation of transcription of a host gene according to the limitations of claim 86. (See *supra*).

For these reasons, the invention of claims1-4, 13, 19-21, 23-35, 37, 41-43, 85-95 and 102 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 1-4, 13, 19-23, 27-35, 37, 41-43, 85-95 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooddell et al. (effective filing date 15 October 2001) US Pub. No. 2003/0143740 in view of Chung et al. (*supra*).

The limitations of independent claims 1 and 85 are described herein above. Wooddell et al. teaches a transposon comprising a transcriptional unit comprising exogenous DNA for introduction into a cell. (See especially ¶¶0014-0015, Figure 1 and the caption thereto). Wooddell et al. further teaches that the transposons disclosed therein are to be used in processes of gene therapy and in the production of stable cell lines. (See especially ¶0046.)

Wooddell et al. does not teach that the transposon comprises insulator elements or a means for preventing regulation of transcription of host nucleic acid by the transcriptional unit.

As described herein above, Chung et al. teaches an insulator element from the chicken β-globin locus and its use in constructs for introducing exogenous nucleic acid into cells. Chung et al. further teaches that the preferable placement of the insulator elements is on both sides of a

gene (i.e., flanking; see especially col. 10, 56-63). Still further, Chung et al. teaches that the use of insulator elements as described therein is particularly advantageous in the production in gene therapy applications and to establish cell lines. (See, e.g.: col. 10, ll. 28-32 ("By insulating a gene or genes introduced into the transgenic animal, the expression of the gene(s) will be protected from negative or inappropriately positive regulatory influences in the chromatin at or near the site of integration."); bridging col. 11-12 ("The constructs of the invention would not only insulate a transfected gene or genes from the influences of DNA surrounding the site of integration, but would also prevent the integrated constructs from impacting on the DNA at the site of integration and would therefore prevent activation of the transcription of genes that are harmful or detrimental to the cell."); col. 23, ¶3 ("By insulating a gene to be transfected with the insulator element of the present invention, the gene could be maintained in an active state." Thereby, overcoming one of the main problems of current gene therapy techniques.); col. 23, ¶4 ("Another problem of gene therapy is the danger that the enhancer or regulatory element of the transfected gene, when integrated in close proximity to an oncogene, may actually promote tumor formation. Again, by insulating the transfected gene with the chromatin insulator element of the invention, the enhancer or regulatory elements of the transfected gene may be prevented from influencing the expression of critical endogenous genes whose activities may be harmful or detrimental to the host."); and ¶ bridging col. 23-24 ("The insulator element also promises to be a useful tool...in the production of stably transfected cell lines. Most frequently, integration of a transfected gene or construct into host cell genome occurs at random. Because the expression of a stably transfected gene is influenced by adjacent regulatory elements near the site of gene integration, insulating the transfected gene with the insulator elements of the present invention

eliminates the variability that is caused by cell-to-cell differences in integration position and in the random sites of integration.")

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transposon taught by Wooddell et al. by the inclusion of a chicken β-globin insulator element flanking the transcriptional unit as taught by Chung et al.

Motivation to combine the elements taught in the prior art comes from the teachings of Wooddell et al. indicating that the transposons described therein are to be used in the production of transformed cells and in gene therapy, and comes from the teachings of Chung et al. indicating that the inclusion of insulator elements provides a number of advantages in each of the intended uses identified by Wooddell et al. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the technologies in view of the effectiveness of the insulator element of Chung et al. in various constructs, including a transposon. (Id.)

For these reasons, the invention of independent claims 1 and 85, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims 2-4, 13, 19-23, 27-35, 37, 41-43, 86-95 and 102 are also found in the cited art. As described above, the insulator element of Chung et al. comprises each of the limitations of claims 3, 4, 13, 19, 88, 89 and 90.

The transposon of Wooddell et al. comprises at least two inverted repeats according to claim 2 (see especially Figure 1 and the caption thereto). Further, Wooddell et al. contemplates a variety of transcriptional units including transcriptional units comprising: a promoter and/or enhancer according to claims 20 and 91 (see especially ¶ 0037); a marker according to claims 21, 41 and 92 (see especially ¶ 0029); a sequence encoding an antisense RNA or siRNA according to

claim 22 (see especially ¶¶0020, 0029 and 0037); a sequence encoding an mRNA according to claim 23; a sequence encoding a therapeutic protein according to claims 42 and 43 (see especially ¶0029); an exogenous nucleic acid according to claim 87; and a DNA according to claim 102.

Both Wooddell et al. and Chung et al. contemplate using constructs comprising the elements disclosed therein to produce cells comprising the constructs, which for the reasons discussed herein above with respect to anticipation by Chung et al. render obvious the cells of claims 27, 29, 31-35 and 93. Furthermore, both Wooddell et al. and Chung et al. contemplate introduction of the constructs into cultured cells according to claims 28 and 94 and contemplate gene therapy which renders obvious the cell in a human of claims 30 and 95. (See *supra*.) In addition, at ¶0021, Wooddell et al. contemplates introducing the construct into a liver cell according to claim 37 and according to the teachings Chung et al., the construct would prevent regulation of transcription of a host gene according to claim 86. (See *supra*).

For these reasons, the invention of claims 1-4, 13, 19-23, 27-35, 37, 41-43, 85-95 and 102 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 1, 13, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Hackett et al. (*supra*) or Wooddell et al. (*supra*) in view of Chung et al. (*supra*) as applied to claims 1 and 13 above and further in view of Pope et al. (1997) *Eur. J. Cancer* 33:1005-1016.

The limitations of claims 1 and 13 and the teachings of Hackett et al. and Wooddell et al. in view of Chung et al. with respect thereto are discussed herein above. Hackett et al. and Chung et al. do not teach a transposon comprising a suicide gene according to the limitations of claims 25 and 26. However, each of Hackett et al., Wooddell et al. and Chung et al. contemplate using the constructs described therein in gene therapy of cancer. (See especially the ¶ bridging pp. 27-28 of Hackett et al. ¶0039 of Wooddell et al. and the ¶ bridging col. 13-14 of Chung et al.)

Pope et al. teaches, "[I]t is also possible to modify tumor cells so that they become sensitive to an agent that is otherwise non-toxic. This involves insertion of a gene coding for an enzyme that converts a non-toxic prodrug into a lethal compound; administration of the prodrug results in the death of the recipient cell []. This approach is know as suicide gene therapy. Suicide gene therapy is an attractive form of cancer gene therapy as the administration of the prodrug results not only in the death of the recipient cell, but also in the death of surrounding cells. Effective therapy can, therefore, be achieved without the need to introduce a functional suicide or prodrug-activating gene into each individual tumor cell. Indeed, a number of studies using suicide genes have shown that it is possible to achieve complete tumour regression even though only a fraction of the tumour mass is genetically modified []" (¶ bridging pp. 1005-1006; citations omitted.)

The teaching of Pope et al. demonstrates that it was known in the art at the time of filing that cancer gene therapy could be effected using suicide genes and that treatment using suicide genes provided the advantage of a "bystander effect" enabling effective therapy without the need to introduce a functional suicide gene or prodrug activating gene into each individual tumor cell. This teaching provides both the suggestion and motivation, in view of the expected benefit of a

bystander effect, to use a suicide gene in the transposon construct of Hackett et al. or Wooddell et al. in view of Chung et al. when the construct is to be used for cancer therapy as contemplated therein. Absent evidence to the contrary, the skilled artisan would have a reasonable expectation of success in combining the elements of the prior art in view of the effectiveness of suicide genes as described in the teachings of Pope et al.

For these reasons, the invention of claims 1, 13, 25 and 26, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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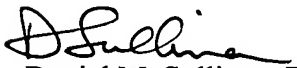

Daniel M. Sullivan, Ph.D.
Primary Examiner
Art Unit 1636

Notice to Comply	Application No. 10/758237	Applicant(s) Hackett et al.	
	Examiner Daniel M. Sullivan	Art Unit 1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

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